Amdt 23 Linda 7/31/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	S. Loosmore, et al.
Appl'n. No.	:	09/210,995
Filed	:	December 15, 1998
Title	:	MULTI-COMPONENT VACCINE COMPRISING AT LEAST TWO ANTIGENS FROM HAEMPHILUS INFLUENZAE TO PROTECT AGAINST DISEASE
Grp./A.U.	:	1645
Examiner	:	Jana A. Hines
Docket No.	:	1038-844 MIS:jb
Date	:	July 23, 2002

BY COURIER

The Commissioner of Patents
and Trademarks,
Box Amendment
Washington, D.C. 20231,
U.S.A.

AMENDMENT

Sir:

This communication is in response to the Office Action of January 24, 2002.

Petition is hereby made under the provisions of 37 CFR 1.136(a) for an extension of three months of the period for response to the Office Action.

Confirmation of entry of the Second Amendment after Final Action filed October 22, 2001 is gratefully acknowledged. As the Examiner noted, claims 6 to 24 are under consideration.

The Examiner rejected claims 6 to 24 under 35 USC 103(a) as being unpatentable over Barenkamp et al (WO 97/36,914) in view of Loosmore et al (USP 5,506,139). Reconsideration is requested.

Claim 6 defines an immunogenic composition for conferring protection in a host against disease caused by *Haemophilus influenzae*, which comprising two components, namely:

> an analog of *Haemophilus influenzae* Hin47 protein having a decreased protease activity which is less than 10% of that of natural Hin47 protein, and
>
> a high molecular weight (HMW) protein of a strain of non-typeable *Haemophilus influenzae*.

The Hin47 protein analog is not an adhesin while the HMW protein is an adhesin. The Barenkamp et al reference describes the HMW protein while the Loosmore et al reference describes the non-proteolytic Hin47 analog. It is the applicants position that neither reference provides the motivation to combine the two immunogens in a single composition as acquired by claim 6.

As the Examiner points out, both references contain the statement:

> "The immunogenic composition of the invention may further comprise at least one other immunogenic or immunostimulating material" (Barenkamp, p. 7, ll 1 to 5; Loosmore, col. 3, ll 63 to 65).

The only "immunogenic or immunostimulating material" identified is an adjuvant, suggesting that the latter materials are preferred additional components, rather than an immunogenic material. In any event, there is no immunogenic material particularly specified in either reference and neither does the Examiner suggest that there is.

The two references also contain the statement:

> "A vaccine which contains antigenic material of only one pathogen is a monovalent vaccine. Vaccines which contain antigenic material of several pathogens are combined vaccines and also belong to the present invention. Such combined vaccines contain, for example, material from various pathogens or from various strains of the same pathogen or from combinations of various pathogens" (p. 22, ll 1 to 8 of Barenkamp; col. 9, ll 14 to 19 of Loosmore).

While suggesting various combinations, there is no suggestion here to combine different proteins derived from the same pathogen, as in applicants claim 6. Again, the references are silent as to any specific combination contemplated.

(The presence of these same passages in the two references is not simply a coincidence, but rather the undersigned attorney wrote both cases).

The Examiner's view is best summarized by the statement in the Office Action that:

> "No more than routine skill was required at the time of appellants invention to combine two well-known compositions, i.e. two different antigens of *H. influenzae*, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for that very same purpose of providing an immunogenic composition."

However, the cited prior art lacks the motivation to do so. As noted above, there are vague, non-specified indications in both references to combine other components with the specific immunogen, but there is no specific indication as to what that other component may comprise, other than an adjuvant (first quotation above) or materials from the pathogens and/or materials from various strains of the same pathogen (second quotation above).

As the Examiner has pointed out, on page 49, lines 15 to 19 of Barenkamp, it is stated:

> ".... the data suggests the HMW adhesin proteins are potentially important protective antigens which may comprise one component of a multi-component NTHI vaccine."

It is conceded that the passage suggests the possibility of combining the HMW adhesin proteins with other *Haemophilus* proteins. However, the passage appears to suggests that only *Haemophilus* proteins which are adhesins are appropriate components. The non-proteolytic analog of Hin47 is not an adhesin (although initially thought to be adhesin, see col. 2, line 17 of Loosmore et al). (It is pointed out that the Examiner is incorrect in the statement that the adhesin protein "should"

comprises one component of the NTHI vaccine. As can be seen from the above quotation, Barenkamp uses the word "may").

Even if the Examiner finds motivation in this passage of Barenkamp to combine the HMW protein with another *Haemophilus* antigen, whether an adhesin or not, such motivation still provdes no motivation to select the non-proteolytic Hin47 analog as the other *Haemophilus* antigen.

As has previously been pointed out to the Examiner, there have been a significant number of *Haemophilus* proteins identified as vaccine candidates besides the HMW and Hin47 analog proteins. These proteins include the various outer membrane proteins A to H, lactoferrin and transferrin receptor protein and the P1, P2, P6 and D15 proteins. It is submitted that there is no motivation provided by the cited prior art why a person skilled in the art would specifically select from all the optional possibilities, the non-proteolytic Hin47 analog to combine with the HMW protein.

The Examiner states in the Office Action, quoting In re Kerkhoven, that:

> "The idea of combining them flows logically from their having been individually taught in the prior art."

The "idea of combining them" does not explain why the two materials should be combined when there is selection available. If the two antigens were the only two known antigens of *Haemophilus influenzae*, then there may be some validity to the position taken by the Examiner, but this is clearly not the case here.

In any event, caution is required when considering combining different antigens into immunogenic compositions because of the danger of impairment of the immunogenicity of the individual components one by the other. As may be seen from applicants data, this phenomenon was observed for increasing amounts of H91A Hin47 when combined with a low dose of rHMW, but disappeared at higher doses of rHMW (see Figure 3).

The Examiner indicates in the Office Action that:

> "Applicant neither argues, nor shows scientific data teaching unexpected results".

It is submitted that such is not the case. Applicants data clearly shows that a synergistic effect can be achieved both in response to the rHMW and H91A Hin47 by combining them. Thus, there is a synergistic effect observed for increasing amounts of rHMW on the primary antibody response to a low dose of H91A Hin47. The H91A H47 improved the primary response to rHMW, if the rHMW was not present in low doses.

These findings are a surprising result, it is submitted. In addition, it is surprising that a single antigen (H91A Hin47) can have both a suppressive and an enhancing effect on another antigen (rHMW) depending on dose of rHMW present. It is further surprising that rHMW would enhance the vigorous antibody response to H91A Hin47, since it is weaker immunogen.

For all these reasons, it is submitted that claims 6 to 24 are patentable over the applied art and the rejection thereof under 35 USC 103(a) as being unpatentable over Barenkamp in view of Loosmore et al.

It is noted that the Examiner continues to assert (and more than once in the Office Action):

> "Barenkamp et al teach complexing additional components to the antigenic composition to enhance immune response including herpes simplex virus vaccine, pseudorabies virus vaccine, tetanus toxoid, poliomyelitis virus vaccine, hepatitis B virus antigen and others (page 24-25, lines 7-10)."

As has been repeatedly pointed out, most recently in the Reply Brief, this is an incorrect statement. As has been repeatedly pointed out, the references to herpes simplex virus vaccine and pseudorabies virus vaccine (page 24, ll. 19 to 21) are made in the context of reporting work done by Lockhoff (USP 4,855,283) using glycolipid analogs as adjuvants, suggesting that such analogs could be used in the HMW-based composition as adjuvants. There is absolutely no suggestion in

Barenkamp of "complexing additional composition to the immunogenic composition" in the form of herpes simplex virus (HSV), as asserted by the Examiner, but rather the possibility to use prior art glycolipid analogs as an adjuvant for the HMW protein is discussed since they have previously been used with HSV.

The references to tetanus toxoid and poliomyelitis virus vaccine (page 24, ll. 28 to 30) are in the context of reporting work performed by Maloney (USP 4,258,029) using octadecyl tyrosine hydrochloride (OTH) as an adjuvant, suggesting that OTH could be used as an adjuvant in the HMW protein containing immunogenic compositions. There is absolutely no suggestion in Barenkamp of combining tetanus toxoid and/or polio vaccine with HMW in an immunogenic composition.

Similarly, the reference to hepatitis B virus antigen (page 24, ll. 31 to 32) is in the context of reporting work performed by Nixon-George et al (ref. 30) using octadecyl esters of aromatic amino acids as an adjuvant, suggesting that such material could be used as an adjuvant in the HMW protein containing immunogenic compositions. There is absolutely no suggestion in Barenkamp of combining hepatitis B virus antigen with HMW in an immunogenic composition.

It is believed that this application is now in condition for allowance and early and favourable consideration and allowance are respectfully solicited.

Respectfully submitted,

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